amendments is attached to this Response at Tab A. A clean copy of all currently pending claims is attached to this Response at Tab B.

By way of review, Applicants have invented a process for the production of vitamin B_{12} by fermentation of *Propionibacterium freudenreichii* cells transformed with a polynucleotide sequence, or a complement thereof, from the endogenous plasmid of *Propionibacterium* LMG 16545.

I. OBJECTIONS

The Examiner has argued that the specification is confusing regarding frequency of transformants that efficiently produce vitamin B_{12}, as well as the actual increase in production of vitamin B_{12} above the level characteristic for non-transformed *Propionibacterium*. Applicants respectfully disagree that the specification is confusing. One of ordinary skill in the art would appreciate from Examples 4 and 5 and from the Table on page 23 that the vector containing the *cobA* gene would result in enhanced vitamin B_{12} productivity in the majority of transformants that are obtained after transformation with this vector. In view of these results, the skilled person would not have any doubt about successful use of the vector to enhance vitamin B_{12} productivity.

Applicants thank the Examiner for pointing out minor errors on pages 5 and 18 of the specification. The specification has been amended to correct these errors. A marked up version and a clean version of these amendments to the specification are attached to this Response at Tabs C and D respectfully. No new matter has been added to the application by way of these amendments to the specification. Applicants will correct any other minor errors in the specification that come to their attention.

II. THE REJECTION UNDER 35 U.S.C. §101

The Examiner rejected Claim 28 under 35 U.S.C. §101, stating that the disclosed invention is inoperative and therefore lacks utility. Specifically, the Examiner argued that Claim 28 is directed to a process for the production of vitamin B_{12} (cobalamin), comprising culturing a host cell containing a polynucleotide that does not contain a gene allowing for cobalamin production.

Applicants have amended Claim 28 to more specifically state that the host cell contains "a sequence that is an endogenous gene of a *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence which is capable of providing for expression of the gene." Support for this amendment is found in the specification at least at page 10, lines 27-32. This amendment more clearly defines the invention and addresses the Examiner's utility concern. In view of the amendment, it is believed that claim 28 is allowable and the rejection should be withdrawn.

what does it mean

what is that

Claim 29 has been deleted. Therefore, the rejection of Claim 29 is moot.

III. THE REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner rejected Claims 28 and 29 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner argued that the phrase "hybridizing selectively" in claim 28 renders the claim indefinite. Applicants have removed this language from the claim in order to address the Examiner's concern and place the claim in condition for allowance.

The Examiner also argued that the term "substantially homologous" renders claim 28 indefinite. Applicants have replaced the phrase "substantially homologous" in claim 28 with the following language: "a sequence that is at least 70% homologous to a sequence as defined under (a), (b) or (d), over a region of at least 100 contiguous nucleotides." Support for this amendment is found in the specification at least at page 4, lines 14-17. This amendment to claim 28 more clearly describes Applicants' invention and addresses the Examiner's concern regarding the definiteness. Claim 28 is now in condition for allowance.

Claim 29 has been deleted. Therefore, the rejection of Claim 29 under 35 U.S.C. §112, second paragraph is moot.

IV. THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

A. Biologic Deposit Requirement

The Examiner rejected Claim 28 part (b) and (c) and Claim 29 are rejected under 35 U.S.C. §112, first paragraph, because the specification is lacking the description of biologic deposit. *Propionibacterium freudenreichii* CBS 101022 and CBS 101023 have been deposited with the International Depository Authority pursuant to the terms of the Budapest Treaty. Copies of International Form BP/4 recognizing receipt of the original deposit for CBS 101022 and CBS 101023 are attached to this Response at Tab E. *Propionibacterium freudenreichii* CBS 101022 and CBS 101023 will be irrevocably and without restriction or condition released to the public upon issuance of a patent arising from the present application.

B. Lack of Written Description

The Examiner rejected Claims 28 and 29 under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner argued that claim 28 is directed to a genus of host cells containing the claimed polynucleotide. The Examiner also argued that claim 28 lacks a description of the function of the nucleotide sequences comprised in said host.

Applicants have amended Claim 28 to claim the *Propionibacterium* species of said host cells. Furthermore, Applicants have also amended polynucleotide sequences listed under (b) – (d) of claim 28 to more clearly describe the nucleotide sequences of the claimed invention. Support for the amendment of the description of sequence (b) of claim 28 is found at least at page 4, line 29 through page 5, line 3. Support for the amendment of the description of sequence (c) of claim 28 is found at least at page 5, lines 5-6 and page 13, lines 17-30. Support for the amendment of the description of sequence (d) is found at least in SEQ ID NO:1. Support for the addition of sequence (e) to claim 28 is found at least at page 4, lines 14-17. Additionally, claim 28 was amended to clarify that in addition to one of sequences (a) through (e), the host cell also contains "a sequence that is an endogenous gene of a *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence which is capable of providing for expression of the gene." Support for this amendment is found at least at page 10, lines 2-32. Clearly, each portion of claim 28 as amended is supported by the written description of the present application.

Claim 29 has been deleted. Therefore, the rejection of Claim 29 under 35 U.S.C. §112, first paragraph for lack of written description is moot.

C. Scope of Enablement

The Examiner also rejected Claims 28 and 29 under 35 U.S.C. §112, first paragraph for lack of enablement. The Examiner argued that the specification does not provide enablement commesurate in scope with claims 28 and 29. Applicants feel that the amendment to claim 28 specifying the *Propionibacterium* species of host cells and more clearly describing the nucleotide sequences (a) – (d), as discussed above, addresses the Examiner's concern. The specification clearly enables a person of skill in the art to make and use the invention described in claim 28 without undue experimentation.

Claim 29 has been deleted. Therefore, the rejection of Claim 29 under 35 U.S.C. §112, first paragraph for lack of enablement is moot.

V. THE REJECTION UNDER 35 U.S.C. §102

The Examiner rejected claim 29 under 35 U.S.C. §102(b) as being anticipated by Ashai et al. Claim 29 has been deleted. Therefore, the rejection of Claim 29 under 35 U.S.C. §102(b) is moot.

VI. CONCLUSION

The Examiner noted that claim 28 contains allowable subject matter. Following the Examiner's suggestion, Applicants have amended claim 28 to more clearly describe the fragments of the p545 plasmid of *Propionibacterium freudenreichii* used for construction of a vector useful in efficient production of vitamin B12 by fermentation of

transformants of *Propionibacterium freudenreichii*. In view of these amendments and the arguments presented above, it is believed that pending claims 28 and 30 are allowable and all rejections should be withdrawn. Favorable reconsideration and allowance of the application claims is therefore courteously solicited.

Respectfully submitted,

McDonnell Boehnen
Hulbert & Berghoff

Dated: March 3, 2003

By: Alison J. Baldwin
Reg. No. 48, 968

Marked-up Version of Amendments to Claims

28. (Twice Amended) A process for the production of vitamin B_{12} (cobalamin), the process comprising culturing a *Propionibacterium* host cell under conditions in which the vitamin is produced and, if necessary, isolating the vitamin, wherein the *Propionibacterium* host cell contains ~~containing~~ a polynucleotide comprising a sequence ~~capable of hybridizing selectively to~~ that is:

(a) SEQ ID NO: 1 or the complement thereof;

(b) a sequence from ~~the 3.6 kb plasmid of *Propionibacterium freudenreichii* CBS 101022~~ SEQ ID NO:1 that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites SalI and AlwN1 or nucleotides 1 to 1800 of SEQ ID NO: 1;

(c) a sequence ~~from the 3.6 kb plasmid of *Propionibacterium freudenreichii* CBS 101023~~that encodes the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70% homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3; ~~or~~

(d) a sequence ~~that encodes a polypeptide which comprises a SEQ. ID. NO: 2 or 3, an amino acid sequence substantially homologous thereto or a fragment of either sequence,~~according to feature (c) that is a fragment from SEQ ID NO: 1 corresponding to position 273 to 1184 or a fragment from SEQ ID NO: 1 corresponding to position 1181 to 1438; or

(e) a sequence that is at least 70% homologous to a sequence as defined under (a), (b) or (d), over a region of at least 100 contiguous nucleotides;

~~under conditions in which the vitamin is produced and, if necessary, isolating the vitamin~~and a sequence that is an endogenous gene of a *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence which is capable of providing for expression of the gene.

39. A process according to claim 2, wherein the endogenous gene of a *Propionibacterium* is the *cobA* gene.

Marked Up Version of Amendments to Specification

Page 5, lines 1-2: This is approximately 1.7Kb in length.

Page 18, lines 5-8: The majority of strains were obtained from the BCCM/LMG culture collection (Ghent, Belgium), although some strains were obtained from ATCC (~~Rockville, Md., USA~~AMERICAN TYPE CULTURE COLLECTION, 10801 University Boulevard, Manassas, VA 20110-2209 (effective March 23, 1998)) or from DSM (Braunschweig, Germany).